

# Flavoxate: present and future

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**Abstract. – OBJECTIVE:** This non-systematic review discusses the available evidence on the use of flavoxate in the treatment of overactive bladder (OAB).

**METHODS:** Medline was searched for inclusion of relevant studies. No limitations in time were considered.

**RESULTS:** Flavoxate hydrochloride is an antispasmodic agent which exerts an inhibition of the phosphodiesterases, a moderate calcium antagonistic activity, and a local anesthetic effect. Results from preclinical and clinical studies show that flavoxate significantly increases bladder volume capacity (BVC), with greater results if compared to other drugs such as empronium bromide and propantheline. Moreover in clinical trials, both versus placebo or versus active comparators, flavoxate treatment was associated with a significant improvement in different low urinary tract symptoms, such as diurnal and night frequency, urgency and urinary incontinence, suprapubic pain, dysuria, hesitancy and burning. In addition flavoxate was associated with an overall more favourable safety profile than competitors.

**CONCLUSIONS:** Several researches and a number of years of clinical practice have proven the efficacy and tolerability of flavoxate administration in the treatment of OAB and associated symptoms. However, new studies are necessary to collect more evidence on the role of this molecule in the treatment of OAB and to further explore its use in other indications such as symptomatic treatment of lower urinary tract infections.

*Key words:*

Flavoxate, OAB, Urodynamics, Lower urinary tract infections.

## Introduction

Overactive bladder (OAB) syndrome is defined by the International Continence Society (ICS) as 'urgency, with or without urge incontinence, usually with frequency and nocturia in absence of an underlying metabolic or pathological

condition<sup>1,2</sup>. This condition has a high prevalence, which has been estimated to be 17%-32% in the general population<sup>3-7</sup>. The prevalence of OAB increases with age, and reaches 40% in subjects aged > 75 years<sup>4,8</sup>, and is higher in men of Afro-American or Hispanic ethnicity<sup>9</sup>.

A marked proportion of patients with OAB (up to 68% according to the recent EpiLUTS survey) experience a marked deterioration in health-related quality of life (QoL)<sup>10-13</sup>. In particular, important reductions in mental health, with a possible association with anxiety and depression, health perceptions and sexual health have been reported<sup>10,14-15</sup>. Patients affected from OAB show increased pain when compared with unaffected controls<sup>13</sup>. Moreover, about 30% of patients with OAB suffer from incontinence<sup>16</sup>, and OAB is frequently associated with infections of the low urinary tract<sup>17</sup>. Lastly, OAB results in lower levels of work productivity<sup>18</sup>.

The above-mentioned consequences of OAB are particularly evident in the elderly<sup>19</sup>. In addition, there are a number of other consequences: for instance, urinary urgency, nocturia and incontinence may be associated with an increased occurrence of falls and fractures. Therefore, healthcare costs related to OAB will increase with the increasing life expectancy of the population<sup>20</sup>.

Treatment of OAB may consist of behavioral training (prompted voiding, bladder training, pelvic muscle rehabilitation), non-pharmacological measures such as transcutaneous electrical nerve stimulation, catheterization, and use of absorbent pads, and pharmacological therapy<sup>17,21</sup>. In particular, pharmacological treatment for OAB is based on a number of medications like darifenacin, flavoxate hydrochloride, hyoscyamine, oxybutynin chloride, tolterodine tartrate, trospium chloride, scopolamine transdermal, and solifenacin succinate and the novel fesoterodine fumarate<sup>21,22</sup>.

Despite the availability of multiple pharmacological options, uncertainty remains on the optimal drug of choice<sup>21,23,24</sup>. Anticholinergic agents

are widely used, but when using these agents, it is necessary to adequately consider adverse reactions due to systemic blockade of muscarine receptors, according to the Guidelines issued by Neurogenic Bladder Society<sup>25</sup>.

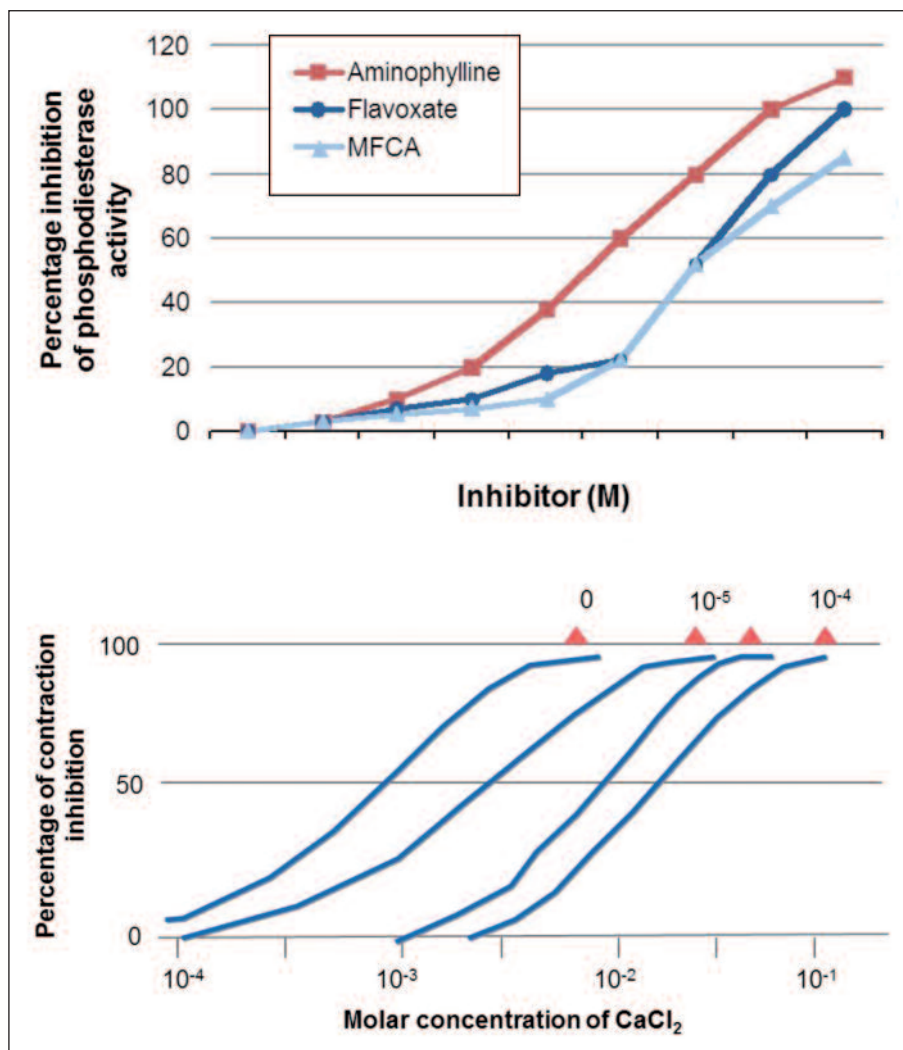
Among different drugs, flavoxate hydrochloride was the first antispasmodic agent to be approved by the FDA for the treatment of OAB<sup>26</sup>. This molecule is widely used in clinical practice, and its efficacy and safety have been tested in several clinical trials. The mechanism of action (MoA) of flavoxate also suggests the potential use of this molecule in indications other than OAB, such as low urinary infections, in combination with antibiotics.

This review will discuss available evidence on the use of flavoxate in the treatment of OAB, and will comment on the potential applications of this drug.

## Criteria for Selection of Evidence

With the aim to identify the key publications on flavoxate for potential inclusion in this paper, a literature search was conducted in the online database Medline using different combinations of pertinent keywords: “flavoxate” AND (“overactive bladder” OR “urinary incontinence”) Only articles written in English language were selected. The search was last updated on the 17<sup>th</sup> May 2013, without any limitation on the publication date.

Articles were selected for inclusion according to their relevance, as judged by the Authors; other references could also be retrieved by manually browsing the reference list of the identified articles, and other papers from Authors' personal collections of literature could be considered as well.



**Figure 1. A**, Inhibition of phosphodiesterase activity in bladder tissue induced by aminophylline, flavoxate and MFCA. **B**, Calcium antagonist activity of flavoxate on Guinea Pigs.

## Mechanism of Action

Flavoxate, administered as a prodrug (flavoxate hydrochloride), acts as a direct spasmolytic on smooth muscle and maintains anticholinergic as well as local analgesic properties<sup>21</sup>. This drug exerts an inhibition of the phosphodiesterases, a moderate calcium antagonistic activity, and a local anesthetic effect<sup>27</sup>.

In particular, the phosphodiesterase enzymes play a key role in the activity of the detrusor muscle of the bladder; therefore, the inhibition of these enzymes exerted by flavoxate contributes to a reduction of the contraction of this muscle. Of note, the inhibitory effect of flavoxate on the phosphodiesterase activity in the bladder tissue is greater than that associated with aminophylline, a non-selective inhibitor of phosphodiesterase (Figure 1A)<sup>28-30</sup>.

Flavoxate also presents a calcium antagonist activity, as shown by studies on Guinea Pigs (Figure 1B)<sup>29</sup>. More in detail, flavoxate suppresses carbachol- and calcium ion (Ca<sup>2+</sup>)-induced contractions of isolated detrusor strips in a noncompetitive and a competitive manner, respectively<sup>31</sup>.

In addition, animal studies show that intravenous flavoxate suppresses both initial phasic, and later tonic, bladder contractions induced by electrical stimulation of the distal end of the pelvic nerve<sup>31</sup>. This action abolishes isovolumetric rhythmic bladder contractions and the associated efferent pelvic nerve activity, without any effect on baseline vesical pressure and afferent pelvic nerve activity. When administered in cerebral ventricles or intrathecally, flavoxate abolishes isovolumetric rhythmic bladder contractions. In cats, flavoxate microinjected into the nucleus reticularis pontis oralis – the pontine micturition inhibitory region – inhibited the reflex micturition; however, this effect was not shown when the molecule was injected into the locus coeruleus alpha (pontine micturition center) or locus subcoeruleus (pontine urine storage center)<sup>31</sup>.

These effects are corroborated by local anesthetic action, similar to that exerted by lidocaine. It has been observed<sup>32</sup> that intradermal injections of flavoxate or lidocaine on the back of guinea pigs were able to induce a very similar anesthetic effect, with highly comparable IC<sub>50</sub> values (3.2x10<sup>-3</sup> and 3.8x10<sup>-3</sup> for flavoxate and lidocaine, respectively). The Authors of the study suggested that this anesthetic activity could be linked to a reduction in the electrical activity of bladder and urethra. Of note, flavoxate presents only a very modest – virtually lacking – anticholinergic ac-

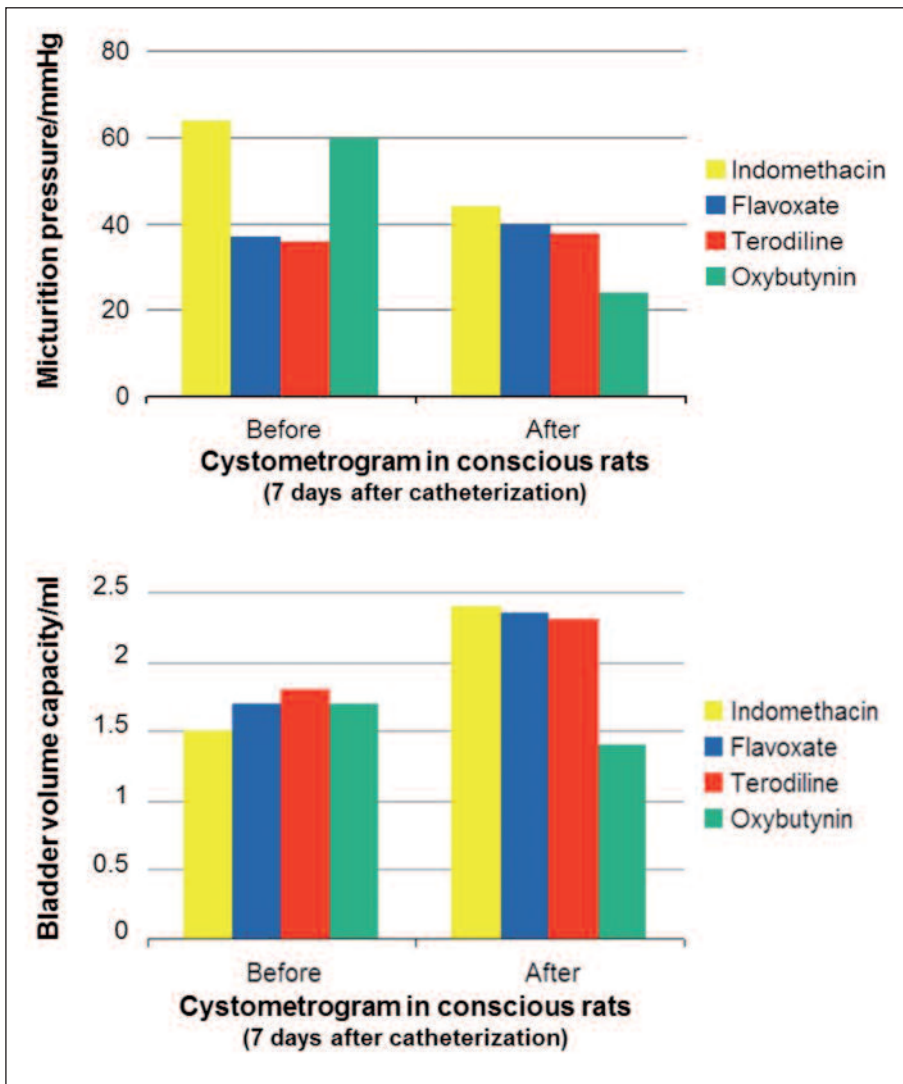
tivity<sup>30,27</sup>. In Guinea Pigs, flavoxate reduced peristaltic motility, endoluminal pressure and longitudinal muscle contractility, thus, showing a myorelaxant effect. In the same test, anticholinergic compounds such as atropine, hyoscine and emepromium failed to relax this tissue. In another series of experiments the effects of flavoxate and anticholinergic drugs on the contraction elicited by vagal electrical stimulation of the guinea-pig isolated stomach *in toto* were assayed: the results obtained suggest that the action of flavoxate is due to direct smooth muscle relaxation and does not involve anticholinergic activity<sup>30</sup>.

## Urodynamic Effects

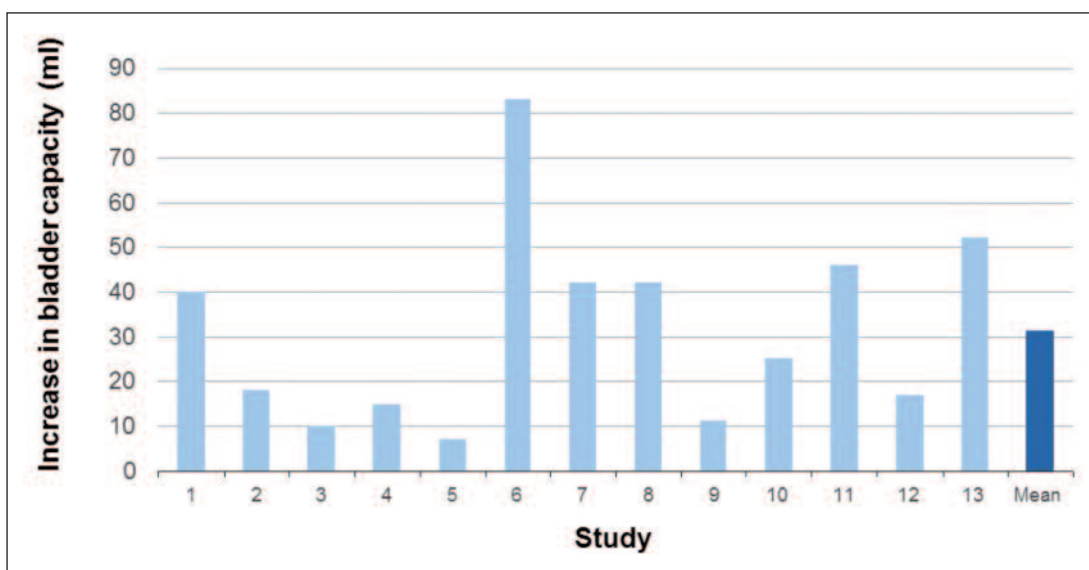
The urodynamic effects of flavoxate were investigated in a number of preclinical studies. More than 30 years ago, a preliminary experimental study<sup>33</sup> showed that both flavoxate and propantheline significantly increased bladder capacity (from 383 ml at baseline to 425 ml with flavoxate and to 550 ml with propantheline). However, the two drugs differed in their effect on residual urine: flavoxate induced a decrease in volume from 60 ml at baseline to 45 ml, while propantheline administration resulted in an increase in residual urine volume, up to 105 ml.

The effects of flavoxate on urodynamics, compared with those associated with other drugs used for the stabilization of the detrusor muscle, were further investigated in a rat model (Figure 2A and B)<sup>34</sup>. More in detail, emepromium bromide, oxybutynin and nifedipine affected, in a dose-dependent fashion, the micturition pressure, with overall modest changes in bladder volume capacity. Terodiline induced significant increases in bladder volume capacity (BVC), but these changes were always not dose-dependent. Indomethacin significantly increased BVC and determined a modest reduction in micturition pressure, but these effects were not dose-related. Only flavoxate induced significant increases in BVC, without any dose-effect relationship; in addition, this molecule did not determine any change in micturition pressure.

The marked urodynamic effects of flavoxate have also been observed in men. In total, 13 human urodynamic studies have been performed with flavoxate<sup>35-47</sup>. Overall, all studies were consistent in showing an increase in BVC associated with flavoxate administration (Figure 3). In particular, a comparative study which analyzed sev-



**Figure 2. A,** Effects of flavoxate and other drugs for detrusor stability on micturition pressure in rats. **B,** Effects of flavoxate and other drugs for detrusor stability on bladder volume capacity in rats.



**Figure 3.** Increase in bladder capacity reported in 13 urodynamic studies in flavoxate-treated patients.

eral hundred cases of motor urge incontinence in females showed that the increases in BVC associated with flavoxate were greater than those reported with emepronium and propantheline. An increase in bladder capacity was observed<sup>40</sup> in 56%, 44% and 50% of patients treated with flavoxate, emepronium and propantheline, respectively. However, the average increase registered with flavoxate (83 ml) was remarkably higher than those observed with emepronium (39 ml) or propantheline (28 ml).

The increase in bladder capacity determined by flavoxate was evident also when considering first urge to void<sup>43,44,46,48</sup>. In particular, a 4-week double-blind, randomized trial in 27 patients showed that flavoxate at both 1200 mg/day and 600 mg/day dosages determines a 40 ml increase in bladder volume at first urge to void<sup>43,44</sup>, and overall similar results were observed in the other studies which investigated this parameter<sup>46,48</sup>.

Lastly, a small study, only published in an abstract form<sup>49</sup>, to our knowledge, showed that flavoxate was associated with a reduction in post-void residual volume, although this effect was greater in males than in females.

### Clinical Evidence

The MoA of flavoxate and its effects on bladder urodynamic represent the basis for its clinical efficacy, which has been extensively investigated in a number of comparative studies versus placebo or active comparators. In addition, two well-conducted uncontrolled experiences have been published and one meta-analysis has explored the use of flavoxate in the treatment of OAB.

### Studies Versus Placebo

Overall, 8 studies versus placebo have been conducted to date; they included more than 700 patients with different conditions, who were treated over a period of 6-28 days. The results observed in these trials, in terms of success rate achieved with either flavoxate or placebo, are summarized in Table I<sup>36,39,50-54</sup>.

In a study by Servadio<sup>36</sup>, patients affected by either cystitis or urethrotigonitis were treated with flavoxate 200 mg tid or placebo. More than 50% of flavoxate-treated patients reported a “very good” or “moderate” response – and 47% a “very good” response – versus 32% of those assigned to placebo. Moreover, flavoxate treatment induced a statistically significant increase in bladder capacity ( $p < 0.01$ ) and a decrease in bladder pressure ( $p < 0.01$ ), and it was overall associated to a significant improvement in several symptoms, such as diurnal and night frequency, urgency, suprapubic pain, dysuria, hesitancy and burning.

The placebo-controlled study conducted by Akasaka et al<sup>53</sup> on 120 subjects affected by frequency and urgency of urination, sense of residual urine and discomfort upon urination led to similar results. Overall response rate with flavoxate was 80% – with 48% “excellent” or “good” responses – compared with a 52% response rate achieved with placebo; in addition flavoxate was more effective than placebo in reducing individual symptoms.

Baert<sup>51</sup> evaluated the use of flavoxate in 60 patients suffering from painful conditions of the lower urinary tract, arising from inflammation and/or infection or from spasm following diagnostic or therapeutic procedures. A significant improvement was noted in frequency and supra-

**Table I.** Success rates of placebo-controlled trials on flavoxate.

Study	Success rate		p value
	Flavoxate	Placebo	
Servadio, 1974 <sup>36</sup>	60%	26%	n.a.
Wehnert and Sage, 1989 <sup>39</sup>	n.a.	n.a.	n.a.
	(+142% score improvement)	(+73% score improvement)	
Yoshida and Kazuko, 1975 <sup>50</sup>	55%	28.6%	< 0.05
Baert, 1974-1975 <sup>51</sup>	n.a.	n.a.	n.a.
	(discontinued for inefficiency 6)	(discontinued for inefficiency 12)	
Fukushige, et al 1975 <sup>52</sup>	83.4%	58.8%	< 0.01
Akasaka, et al 1975 <sup>53</sup>	80%	51.7%	0.005
Miyazaki, et al 1975 <sup>35</sup>	80%	52.1%	< 0.05
Sonoda, et al 1975 <sup>54</sup>	59.3%	18.7%	< 0.05

n.a.: not available

pubic pain, and marked relief of dysuria, hesitancy and burning was also reported, thus supporting the effect of flavoxate on different low urinary tract symptoms.

Overall similar results on flavoxate effects were observed in other placebo-controlled trials<sup>35,39,50-52,54</sup>.

### **Studies Versus Active Comparators**

Flavoxate has been studied in several controlled and open label studies against active comparators including emepronium, propantheline, butylscopolamine, oxybutynin, phenazopyridine, propiverine (Table II)<sup>33,39,40,54-59</sup>.

Stanton<sup>55</sup> compared the efficacy and tolerability of flavoxate 200 mg and emepronium 200 mg in the treatment of 38 patients with urinary incontinence affected by either detrusor instability or sphincter dysfunction. The results of this randomized study showed that flavoxate was more effective than emepronium in decreasing stress incontinence, relieving symptoms of urgency and in reducing diurnal frequency. Overall, 86% of patients receiving flavoxate experienced an improvement in urinary incontinence, versus 66% of those assigned to emepronium; however, the difference did not reach statistical significance. Flavoxate was also more effective than emepronium in reducing intravesical pressure and in increasing overall bladder capacity, even though the difference did not reach statistical significance. Neither drugs produced any significant increase in residual urine.

Flavoxate was also associated with a higher success rate than propantheline in three comparative studies<sup>33,40,56</sup>. Overall, the success rate determined by flavoxate therapy was 50% or higher, versus 15-30% reported with propantheline.

Gaudenz and Weil<sup>40</sup> reported the results of a comparative study on more than 100 women affected from motor urge incontinence, treated with either flavoxate 200 mg tid, propantheline 30 mg tid or emepronium 200 mg tid. The therapeutic responses were 50% with flavoxate, 44% with propantheline and 34% with emepronium, with an overall higher response rate achieved with flavoxate. Flavoxate was also associated with a higher percentage of cure or improvement of the main symptoms associated with motor urge incontinence, such as urgency incontinence, urinary frequency, urgency imperative, nocturia and stress urinary incontinence. Bladder capacity was also increased by all three drugs, with a slightly better result achieved with flavoxate: 56% versus 50% with propantheline and 44% with emepronium.

Similar results were disclosed in another study on 20 patients affected by urgency, frequency and urge incontinence, who were administered either flavoxate 200 mg qid or propantheline 30 mg qid. The results showed that the clinical effect of flavoxate was comparable to that of propantheline in terms of therapeutic response and increase in the overall bladder capacity. However, only flavoxate determined a reduction in residual urine volume, while propantheline produced a marked rise of this parameter (up to 105 ml)<sup>33</sup>.

In a randomized controlled trial on 43 patients, Herbst<sup>56</sup> reported an overall therapeutic response of 52% with flavoxate 200 mg qid, compared with 27% achieved with propantheline 15 mg qid<sup>56</sup>. Similar findings were reported when comparing flavoxate with butylscopolamine (success rate 59-65% with flavoxate vs 42-44% with butylscopolamine)<sup>54,57</sup> and with oxybutynin (82% vs 65-79%, respectively)<sup>58</sup>.

In particular, Nijima et al<sup>57</sup> performed a double-blind controlled trial to investigate the effects of flavoxate and butylscopolamine on neurogenic frequency and irritable bladder. Overall, flavoxate showed a marked therapeutic effect, with a more evident improvement in urination, urinary urgency and discomfort after urination than butylscopolamine. Flavoxate was also superior in the treatment of urinary incontinence, while no differences were reported between the two drugs in terms of amount of residual urine.

Flavoxate 1200 mg/day was also compared to oxybutynin 15 mg/day in a randomized trial<sup>58</sup> on 50 women with motor or sensory urgency. Results showed a higher therapeutic response achieved with flavoxate, with 82% of patients cured or improved, compared with 79% reported with oxybutynin. In addition, flavoxate was associated with a more marked decrease in several symptoms such as incontinence, urgency, pads use and dysuria, and it was overall preferred by 61% of patients.

Another analysis of nine clinical trials<sup>59</sup>, conducted in the '70s, showed a numerically higher success rate with flavoxate than with phenazopyridine, in patients with prostatitis (66% vs 31%) or other urinary disorders (80% vs 56%). Similarly, the evaluation of symptom-severity performed after two and five days of therapy revealed that the majority of symptoms improved in a higher percentage of patients on flavoxate therapy than in those treated with phenazopyridine.

Wehnert and Sage<sup>39</sup> accomplished a cross-over, placebo-controlled study on 46 patients suffering from urgency/urge incontinence, who were treated with propiverine 45 mg/day and flavoxate 300 mg/day for 4 weeks. Both groups showed a significant reduction of micturition frequency and an increase in compliance, whereas the placebo was ineffective. Both agents were associated with a similar improvement of symptoms or urgency/urge incontinence.

### **Uncontrolled Experiences**

Fehrmann-Zumpe et al<sup>60</sup> studied the efficacy of flavoxate in an observational study conducted on 1,800 patients with urge incontinence treated with flavoxate over a period of 2 weeks. A subgroup of 618 patients without urinary tract infections or benign prostatic hyperplasia were treated with flavoxate only, and showed a reduction of dysuria (37%), nocturia (53%), and both daytime (61%) and nighttime urge (69%). Bladder volume at first urge sensation increased by 36%. In 89.2% of all patients the residual urine volume was stable or decreased. Both groups showed better results with flavoxate qid (800 mg) compared to tid (600 mg).

In another unblinded, uncontrolled clinical study, Gu et al<sup>61</sup> studied flavoxate on 361 patients with urgency/incontinence. Patients received flavoxate 200 mg tid, orally, for 2 weeks (although 33 patients received a daily dosage of 1.200 mg). Overall, among 336 evaluated patients, 228 (67%) were completely cured of urgency/incontinence symptoms, 66 (20%) were improved and 42 (13%) did not report any change. Flavoxate was also effective in 77.4% of patients who were refractory to previous anticholinergic treatment.

### **Meta-Analysis**

A Cochrane meta-analysis<sup>23</sup> evaluated 12 trials on the treatment of OAB in adults, among which nine trials compared flavoxate with anticholinergic agents. Overall, there was no evidence of a difference in cure rates between anticholinergics and flavoxate: most of the studies reported no statistically significant difference between the two drugs, while some studies suggested that patients actually preferred flavoxate treatment but objective assessment with urodynamics was equivocal. One study reported no difference in the number of patients affected from nocturia after treatment. With respect to tolerability, three studies reported worse adverse

events in the anticholinergic groups, while in the remaining four trials significant differences between flavoxate and anticholinergic drug were observed, with more adverse effects registered in the anticholinergic group. However, the Authors of this analysis concluded that there is inadequate evidence as to determine whether flavoxate is better or worse than anticholinergic medications.

### **Safety Profile**

To date, all studies agree that the flavoxate treatment of OAB is well tolerated. It causes no additional adverse consequences due to residual urine and it is not associated with risks of ventricular arrhythmia<sup>62</sup>.

Available data show that the occurrence of all-grade adverse events ranges from 3.9% with the 600 mg/day dosage to 5.0% with the 1200 mg/day dosage, and only sporadic severe adverse events (n=8 in the period 2008-2010) related to study drug were reported (Figure 4) (data on file).

Flavoxate was also associated with an overall more favourable safety profile than competitors in a number of head-to-head studies<sup>33,40,44,56,57</sup>. Compared with oxybutynin, flavoxate was associated with a significant lower percentage of side effects: 26.8% versus more than 90% observed with oxybutynin<sup>44</sup>. Also when compared with propantheline or emepronium, flavoxate had a favourable tolerability profile, ranked as “good” in nearly 90% of the cases<sup>33</sup>. In addition, prophantheline was associated with a higher prevalence of side effects such as difficulties in urination, blurred vision and dry mouth, which were absent or rare with flavoxate treatment<sup>33</sup>.

Of note, in the comparative study by Gaudenz et al<sup>40</sup> no withdrawals were reported for patients treated with flavoxate, while the percentages of withdrawal for safety reasons were 11% and 8% for propantheline and emepronium, respectively. The tolerability of flavoxate is further supported by the results of the large Cochrane meta-analysis of anticholinergic drugs versus other medications for OAB in adults<sup>23</sup>. Statistical analysis demonstrated how flavoxate was associated with a reduced risk of adverse events than anticholinergic agents (Relative Risk: 2.28; 95% Confidence Interval 1.45-3.56).

Table II. Main characteristics and results of controlled trials on flavoxate versus active comparators.

Study	Design	Population	Treatment	Outcomes	Tolerability
Stanton, 1973 <sup>55</sup>	Randomized, double blind, cross over trial	n=38, with urinary frequency, urgency and incontinence	Flavoxate 200 mg t.i.d	Therapeutic response: 86% Improvement in stress incontinence: 62.5% Relief of urgency: 66.5% Intravesical pressure: - 9 cm H <sub>2</sub> O Bladder capacity: + 59 ml Therapeutic response: 66% Improvement in stress incontinence: 30.5% Relief of urgency: 51% Intravesical pressure: - 5.6 cm H <sub>2</sub> O Bladder capacity: + 15.6 ml	Drowsiness: 1 pt Bloated feeling: 1 pt Depression: 1 pt  Nausea: 3 pts Blurred vision: 3 pts Bloated feeling: 1 pt Dry mouth: 1 pt Headache: 1 pt
Gaudenz and Weil 1980 <sup>40</sup>	Comparative trial	n= 122, with motor urge incontinence	Emepronium 200 mg t.i.d  Flavoxate 200 mg t.i.d	Therapeutic response: 50% Inhibition of destrusor contraction: 25% Increased bladder capacity: 56% , +83 ml	Drug tolerance: 88%
11%			Propantheline 30 mg t.i.d	Therapeutic response: 15% Inhibition of destrusor contraction: 14%	Drug tolerance: 54% Discontinuation of the drug:
			Emepronium 200 mg t.i.d	Increased bladder capacity: 44%; +28 ml Therapeutic response: 34% Inhibition of destrusor contraction: 17% Increased bladder capacity: 50%; +39 ml	Drug tolerance: 59% Discontinuation of the drug: 8%
Pedersen, 1977 <sup>33</sup>	Randomized single blind, cross-over trial	n= 20, with frequency (n=18), urgency (n=19) and (n=18) urge incontinence	Flavoxate 200 mg q.i.d  Propantheline 30 mg q.i.d	Therapeutic response: 50% Bladder capacity: + 42 ml Residual urine: -15 ml Therapeutic response: 30% Bladder capacity: + 167 ml Residual urine: + 90 ml	Difficulty in voiding: 5%  Difficulty in voiding: 30%
Herbst, 1970 <sup>56</sup>	Randomized controlled trial	n= 43	Flavoxate 200 mg q.i.d - 1 wk  Propantheline 15 mg q.i.d - 1 wk	Therapeutic response: 52%  Therapeutic response: 27%	Dry mouth/throat: 1 pt Difficulty in concentrating: 1pt Dizziness: 1 pt Dry mouth/throat: 13 pts Blurred vision: 1 pt Difficulty in urinating: 1 pt Drowsiness: 1 pt Headache: 1 pt

Table continued



**Table II.** Main characteristics and results of controlled trials on flavoxate versus active comparators.

Study	Design	Population	Treatment	Outcomes	Tolerability
Sonoda, et al 1975 <sup>54</sup>	Comparative trial	n.a.	Flavoxate	Therapeutic response: 59%	n.a.
Nijijima, et al 1975 <sup>57</sup>	Double blind comparative trial	n= 101, with neurogenic frequency and irritable bladder	Butylscopolamine Flavoxate 200 mg t.i.d Butylscopolamine 20 mg t.i.d.	Therapeutic response: 42% Therapeutic response: 64% Therapeutic response: 44%	n.a. Side effects: 18.8% Side effects: 25%
Scalabrino, et al 1988 <sup>58</sup>	Randomized controlled trial	n.a.	Flavoxate 1200 mg/day Oxybutynin 5 mg t.i.d.	Therapeutic response: 82% Therapeutic response: 65%	n.a. n.a.
Milani, et al 1993 <sup>59</sup>	Randomized, cross-over multi center trial	n= 50, female with motor or sensory urgency	Flavoxate 1200 mg/day	Therapeutic response: 82% Mean change in symptoms score*: 0.78 Incontinence: 1.05 Urgency: 0.66 Pads: 0.59 Dysuria: 0.072	Side effects: 22% Dry mouth: 2% Abdominal or stomach pain: 24%
Gould, 1975 <sup>60</sup>	Comparative trial	Pts with prostatitis or other urinary disorders	Oxybutynin 15 mg/day Flavoxate	Therapeutic response: 79% Mean change in symptoms score*: 0.83 Incontinence: 0.9 Urgency: 0.92 Pads: 0.71 Dysuria: 0.072	Side effects: 84% Dry mouth: 78% Abdominal or stomach pain 36%
Wehnert and Sage 1989 <sup>59</sup>	Cross-over trial	n= 46, urgency/urge incontinence	Phenazopyridine Flavoxate 300 mg/day Propiverine 45 mg/day	Therapeutic response: 66% (prostatitis), 80% (others) Therapeutic response: 31% (prostatitis), 56% (others) n.a. n.a.	n.a. n.a. n.a.

\* Symptoms score: diurnal and nocturnal frequency, incontinence, urgency, dysuria and pad use, evaluated from 0 = best to 2 = worst; qid: four times a day; pt: patient; pts: patients; tid: three times a day.

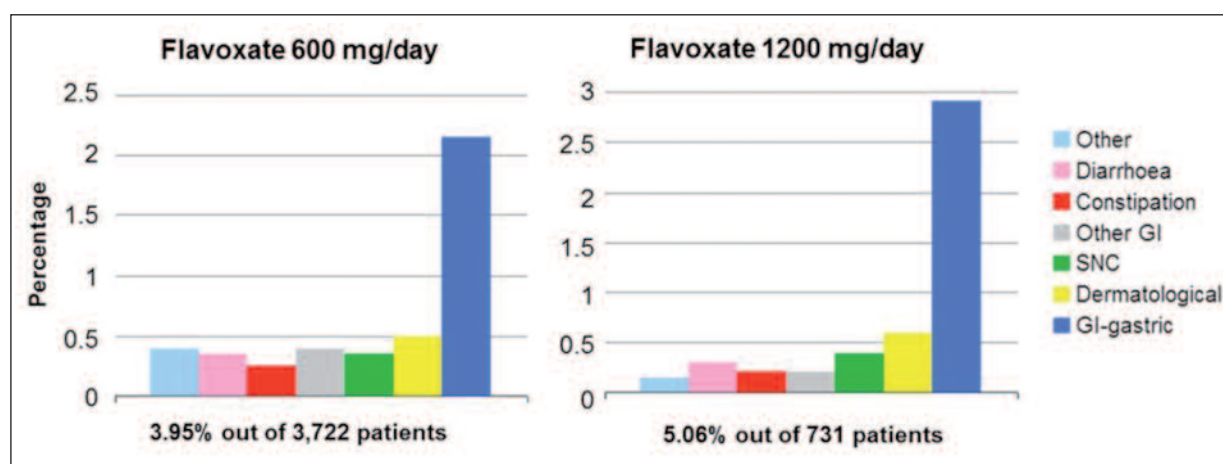


Figure 4. Occurrence of all-grade adverse events with flavoxate 600 mg/day or 1200 mg/day.

### Expert Opinion

Flavoxate was the first antispasmodic agent to be approved by the FDA for the treatment of OAB, and since its approval it has been largely used in clinical practice: ‘field-practice’ experience on this molecule is broad. Available pharmacovigilance data show that up to December 2010 more than 20,210,000 patients have been treated with flavoxate (Recordati S.p.A., Milan, Italy, data on file).

Flavoxate has been tested on different populations of patients in a number of clinical studies, which proved its efficacy and tolerability in the treatment of OAB and associated symptoms. However, despite evidence collected from those studies seems well-grounded, it is necessary to point out that most studies have been conducted more than 20 years ago, were of limited sample size, and compared flavoxate with other medications which are no longer used in clinical practice. On these bases, the Authors of the most comprehensive Cochrane Review conducted on OAB treatments<sup>23</sup> and the recommendations issued by the 4<sup>th</sup> International Consultation on Incontinence<sup>62</sup> concluded that, despite the favorable results shown in clinical trials, there is currently not enough evidence to clearly identify the role of flavoxate in the treatment of OAB.

A consensus on the optimal pharmacological treatment of OAB however still lacks. This undefined scenario suggests the need of new, well-grounded pieces of evidence on the use of flavoxate and other molecules for the treatment

of this bothersome condition. While this evidence appears eagerly awaited, we believe that there is a place for flavoxate in clinical practice.

In fact, clinical experience on flavoxate in routine daily practice is wide; although the efficacy of this molecule seems at least not-inferior than the efficacy of other agents used in the same setting, the good tolerability profile shown by flavoxate should be taken into account when selecting an agent for OAB. Only a few adverse events have been reported with the use of flavoxate such as nausea, vomiting, dry mouth, headache, dizziness, blurred vision, and nervousness. However, caution is recommended when the drug is given to patients with glaucoma, as, like all anticholinergic drugs, flavoxate may present the risk of precipitating angle closure glaucoma<sup>63</sup>. Administration of the drug during pregnancy/lactation should also be avoided.

Interestingly, the peculiar MoA of flavoxate might suggest the possible use of this molecule in indications other than OAB. For instance, we speculate that the prompt local anesthetic and urodynamic effects exerted by flavoxate can have a role in the symptomatic treatment of lower urinary tract infections, while antibiotics exert their microbicidal action. Similarly, flavoxate, thanks to its analgesic effect, can help control pain and discomfort during bothersome interventional procedures such as catheterization. We do believe that *ad hoc* trials are needed to investigate these intriguing hypotheses, which – if confirmed – will add further ground for a wider use of flavoxate in clinical practice.

## Conclusions

Flavoxate appears as a well-established drug in the current treatment scenario of OAB; more evidence is anyhow required to further explore its use in this and – potentially – in other indications.

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## Conflict of interest

The Authors declare that there are no conflicts of interest.

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